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The extent and location of intra- and sub-retinal fluid as prognostic factors for the outcome of patients with optic disc pit maculopathy.

Short title: Outcome of optic disc pit maculopathy

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Key words

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Synopsis

A retrospective case note review of 36 patients with optic disc pit maculopathy showed that there was a worse visual and anatomical outcome in those cases with subretinal and multi-layered intra retinal fluid as well as cases with fluid extending at least as far as the major vascular arcades.

Abstract

Purpose: To determine if baseline fundoscopic and optical coherence tomography (OCT) features influence the clinical course of optic disc pit maculopathy.

Method: A multicenter, retrospective case note review was undertaken, using standardised OCT and clinical data collection. Visual success was defined as at least a two line visual acuity improvement, anatomic success as full resolution of OCT foveal fluid with restoration of the normal foveal contour, and partial anatomic success as incomplete resolution of the OCT foveal fluid. Outcomes were compared to a synthesis of the literature, using similar eligibility criteria.

Results: Of 36 patients (36 eyes), two spontaneously improved and 34 underwent surgery. Visual success was achieved in 64% of surgical cases, anatomic success in 36% and partial anatomic success in 47%. Cases with multilayer intraretinal and subretinal fluid were less likely to have visual success ($p=0.003$). Cases where the fluid did not extend to the macular arcade vessels also had better visual and anatomical outcomes ($p=0.004$ and 0.005 respectively).

Conclusion: Fundoscopic and OCT features can help predict surgical outcome in ODPM.

Introduction

Despite having been first described in 1927, the pathogenesis and optimal treatment of optic disc pit maculopathy (ODPM) remains poorly understood and ill defined¹. Some cases spontaneously improve and in those that don't the optimal therapy is uncertain. Vitrectomy has been the most commonly recommended surgical treatment with or without several additional steps including laser around the temporal edge of the optic disc, internal limiting membrane (ILM) peeling, subretinal fluid drainage and gas tamponade². In 1996 optical coherence tomography (OCT) confirmed, what had been clinically suspected by Lincoff in 1988, that there is usually a schitic like cavity component to ODPM³⁻⁵. Clinical experience in the OCT era has shown a variety of patterns of fluid distribution with fluid accumulations in the sub ILM space, ganglion cell layer, inner nuclear layer, outer nuclear layer and subretinal space. Recent OCT studies have suggested that fluid typically first accumulates in the outer retinal layers and then spreads to the inner retinal layers and/or subretinal space^{6,7}. Other OCT features such as outer retinal defects at the fovea have also been described⁸. It has been suggested that cases with intraretinal fluid are more resistant to treatment and present at older ages than those with predominantly subretinal fluid (SRF)⁹. Features predictive of outcome would guide clinical decision making in terms of observation and initial treatment choices.

We carried out a retrospective case note and OCT review of ODPM. Specifically, we assessed the relationship between the age of presentation, response to treatment and/or observation with the baseline optic disc pit and OCT appearances to assess whether any features were predictive of the subsequent clinical course and outcome. We also carried out

a literature review to identify cases with similar features, which could be analysed in the same way.

Method

Cases of ODPM managed by the authors over an 11 year period were collated. Cases were identified using the surgical records and personal databases of the surgeons involved. To be eligible, cases had to have a congenital optic disc pit with an associated ODPM, documented by OCT. Cases also had to have both a baseline and final follow up OCT, and at least six months follow up after presentation or any surgical intervention. Cases with orbital and cranial abnormalities, as well as systemic syndromes associated with optic disc pits, were excluded, as were those with prior treatment. The case notes were reviewed by the individual clinicians and used to complete a standardized data collection questionnaire. This included baseline anonymised demographic and clinical data, and subsequent follow up data including any periods of observation and surgical interventions.

The maximum size of the optic disc pit was measured using clock hours and its location categorised by the location of its centre into one of eight zones (temporal, inferotemporal, inferior etc.) by one experienced clinician masked to the outcome. Similarly eyes were grouped into two based on the extent of the fluid associated with the pit: fluid extending up to and beyond the main macular vascular arcades and those where the extent of fluid was less than this. The location of the fluid was classed into 3 groups (Figure 1):

- 1) Subretinal fluid and outer retinal layer fluid (SRF +ORL) or subretinal fluid only. (SRF)

2) Intra-retinal fluid of any location only (IRF)

3) A combination of multi-layered intra-retinal fluid and subretinal fluid. (SRF +MLF)

In all cases the location of the fluid in any part of the maculopathy was used to categorise the final grade. The presence of an outer retinal defect (ORD) at the fovea was noted. This was defined as a central defect in the outer retina of less than full thickness.

Visual acuities were collected by Snellen and converted into logMAR values for analysis. The cases were sorted into those with and without visual success after either observation or treatment on the basis of a ≥ 0.2 logMAR improvement in visual acuity at final follow up. The cases were also defined as having anatomical success if intraretinal and subretinal fluid resolved at the foveal centre with reformation of the foveal profile. Partial success was defined as a reduction in fluid compared with baseline but not complete resolution.

We also carried out a literature review of OCT documented ODPM cases. A PubMed MEDLINE searches were undertaken including all articles until February 2014 using Boolean operators with the following keywords and MESH headings: optic disc pit maculopathy; optic disc pit; optical coherence tomography. Only English articles describing primary research from peer reviewed journals were collected. Abstracts were reviewed by two independent observers and relevant articles for full review were identified. Further articles were identified in the reference lists of retrieved articles. The review identified 29 articles and 98 cases of ODPM which were documented in sufficient quality to undergo pooled, statistical analysis⁹⁻³⁷. To be of adequate quality studies had to provide a defined diagnosis of optic disc pit maculopathy with accompanying details including age and sex of patient,

size and location of optic disc pit and either an OCT image or a description of the OCT image at presentation. Details of periods of observation, treatments carried out and anatomical and visual outcomes were also recorded.

Data analysis was carried out on the current series, and then the cases collected from the literature and finally a combined analysis of cases from both the current series and the synthesis of the literature was carried out.

Statistical analysis

Descriptive and statistical analysis was performed using IBM SPSS Statistics 21. Patients' demographic characteristics, pre- and post-operative variables are presented in terms of mean, standard deviation (SD) and range or percentage as appropriate.

For analysis the SRF +/-ORL fluid group was compared to the IRF only and SRF +MLF groups using independent measures ANOVA with Tukey post-hoc testing for continuous variables. Associations between non-continuous variables were analysed using the Chi-squared statistic using Fisher's exact probability. Statistical significance was considered with a p-value of 0.05 or less.

Logistic regression analyses was performed with the binary outcomes anatomic and visual success with the continuous predictors age, size and pre-operative visual acuity and sex, type of fluid, extent of fluid and presence of ORH as categorical predictors using a forward logistical regression method. Partial anatomic success was coded as success for the analyses.

Results

Thirty six patients (36 eyes) in the current series and 98 patients (98 eyes) from 29 publications in the literature review series were found suitable for inclusion. In some cases only a proportion of the cases from published articles were suitable for inclusion because of missing data. The details of optic disc pit size and location, fluid extent and the presence of an outer retinal defect were infrequently recorded and so were omitted from the synthesis of the literature. The demographic variables, anatomic features and outcomes of the cases are summarised in Table 1.

Current series

The mean age of the patients was 33 years with 21 (58%) being male. There were 15 (42%) left eyes and 21(58%) right eyes. All but 7(19%) were white caucasian in ethnicity.

Of 36 eyes, 16(44%) were categorised as SRF+/-ORL including two cases of SRF only, 8(22%) as IRF only and 12(33%) as SRF + MLF. There was no difference in ages ($p=0.33$), sex ($p=0.68$), pit size ($p=0.31$), pit location ($p=0.89$) or extent ($p=0.32$) between the three different fluid subtypes (Table 2). Similarly there was no relationship between age and pit size at presentation with maculopathy ($p=0.28$)

An outer retinal defect (ORD) was present in 18 (50%) of the cases. It's presence was not associated with the level of pre- or post-operative visual acuity ($p=0.24$ and $p=0.32$ respectively) (pre/post visual acuity with ORD 0.90 (SD 0.49) logMAR / 0.61 (0.42) logMAR respectively, versus pre/post visual acuity without ORD 0.71 (0.46) logMAR / 0.46 (0.36) logMAR).

The symptom duration prior to presentation was recorded in 28 (78%) of the 36 eyes and was for a median of 6 months (SD 11.4, range 1-48 months). There was no relationship between duration of symptoms and either the type of fluid ($p=0.56$), extent of fluid ($p=0.78$) or presence of an ORD ($p=0.90$).

A period of observation was undertaken in 27(75%) of the 36 eyes for a median of 4 months (range 3-48 months) prior to an intervention. During this time three (8%) patients worsened by ≥ 0.2 logMAR, 22(61%) remained stable and two (6%) improved and remained stable for more than 12 months. The two patients who improved had baseline logMAR visual acuities of 0.5 and 0.8 and improved to 0.3 and 0.6 respectively. One had SRF +ORL fluid and one had IRF only.

Prior to invasive surgery 5 patients in total had laser around the optic disc and this was unsuccessful in all cases.

A total of 34(94%) eyes underwent a surgical procedure. This was vitrectomy with gas in 31(91%) eyes, gas and laser without vitrectomy in two (6%) eyes, and vitrectomy and ILM peel alone in one (3%) eye. Additional procedures at the time of vitrectomy were laser in 23 eyes (74% of the eyes undergoing vitrectomy) and ILM peeling in eight eyes. In total nine eyes had vitrectomy without laser. Drainage of SRF was carried out in two eyes. We found no association between any one surgical variable and either anatomic or visual success. (vitrectomy and gas cases summarised in table 2). The case that underwent vitrectomy and ILM peel had visual success but only partial anatomical success. The two cases that had intravitreal gas injection and laser without vitrectomy both had visual success and complete anatomical success. We analysed whether performing laser in cases with SRF at the disc

margin was beneficial compared to those without SRF and again found no significant relationship.

Five patients had repeat surgery. In two of these five cases initial surgery had been a success and recurrence had occurred. The repeat surgery in both these cases was successful. In the other three the repeat surgery was done for initial failure and in all 3 cases there was persistent lack of visual success. There was one other recurrence not treated with further surgery.

Follow up, i.e. the latest date after surgery that the patient was seen after primary surgery, was for a minimum of 6 months with a mean of 26 months (range 6-60 months). This was not statistically significant from the follow up duration in the synthesis of the literature we collected ($p=0.87$) (Table 1).

Final visual success was achieved in 23(64%) of the patients and final anatomic success in 13(36%), with partial success in 17(47%). The mean visual change was +0.28 logMar (SD 0.27) with a range of -0.2 to 1. Pre-operative visual acuity was closely related to post-operative visual acuity (Pearson's correlation coefficient $r=0.83$; 95% confidence interval [CI] 0.68-0.91). There was a significant difference between the presenting visual acuity in those with SRF + ORL fluid compared to SRF + MLF ($p=0.05$) but not between the IRF only group and the other two groups.

Follow up duration did not affect the chances of either visual or anatomic success ($p=0.84$ and 0.74 respectively)

There was no relationship between the fluid location and anatomic success ($p=0.18$) but there was a significant association between fluid location and visual success ($p=0.003$).

Table 3 summarises the three fluid subtypes in the current series, showing their demographics, anatomic and visual results.

The extent of fluid also had a significant relationship with both visual and anatomic success ($p=0.004$ and 0.005 respectively). Cases with more extensive fluid had worse outcomes.

Using multiple logistic regression analysis with visual success as the outcome, there was a significant association between the type of fluid on OCT and visual success with SRF + MLF having lowest chance of success. Patients with SRF + MLF had significantly decreased odds of visual success (odds ratio 0.03, 95% CI 0.003-0.42) as compared to other fluid subtypes. Similarly, there was also a significant association with the extent of fluid with an odds ratio of 0.07 (CI 0.007-0.65) for visual success. There were no other significant associations with outcome.

Cases collected from literature and combined dataset

Analysis of both the literature cases only and the combined dataset confirmed the association of the location of the fluid in terms of visual success with a higher chance of success in the SRF+ORL group and a lower chance of success in the SRF+MLF group ($p=0.011$ and $p=0.004$ respectively). This relationship also existed for anatomical success ($p=0.032$ and $p=0.014$ respectively)

Discussion

There have been several reports describing the occurrence, features and treatment of ODPM but these have generally been on small numbers and few have addressed the issue of prognosis and response to treatment. The possibility of OCT features being predictive of outcome is particularly interesting as several different patterns of sub and intraretinal fluid

associated with optic disc pit maculopathy have been described. Roy et al. presented a series of 32 eyes with ODPM and added another 46 eyes from the literature to provide figures on the occurrence of these different patterns. They found that 28% of eyes presented with SRF and ORL fluid, 46% with SRF and multilayer fluid, 21% with IRF only and only 4% with SRF only, which is in broad agreement with the percentages found in our study.⁶ It is interesting however that in the cases we collected from the published literature (table 1) there were more with SRF and ORL fluid which may be accounted for by different case mixes or alternatively publication bias.

We found that the pattern of distribution of fluid on OCT (Figure 1) was predictive of outcome. Patients with SRF and multilayer fluid had worse outcomes than those with SRF and ORL fluid only. This was shown for visual outcomes in our own data and for both visual and anatomic outcomes in the literature only and combined dataset, strengthening the validity of the finding. This concurs with the findings of Skaat et al., whose study of five patients found that those with multilayer fluid patterns had a worse prognosis than those with SRF and ORL fluid.⁹ We also found that patients with fluid extending beyond the vascular arcades had worse outcomes than those with less extensive fluid. One possible explanation of both these negative prognostic indicators is that both are associated with longer duration disease. Unfortunately the duration of reduced vision was not clearly defined in some cases, but in the cases where it was there was no significant correlation between duration and the extent and type of fluid. We did however find that patients with SRF + MLF had worse presenting visual acuities than those with SRF + ORL fluid.

Jain and Johnson have recently reviewed the pathogenesis of ODPM and concluded that it likely relates to the presence of a scleral or lamina cribrosa defect permitting the anomalous communication of fluid between the intraocular and extraocular spaces.² Another possible explanation therefore is that multilayer fluid, and a greater extent of fluid, are related to a larger, and a likely more difficult to close, scleral defect. There was however no association between pit size in terms of clock hours of the optic disc and the type or extent of fluid. Fundoscopic disc pit size does not appear to be related to the extent of the scleral communication. Similarly, although Skaat et al. suggested that patients presenting with MLF were older than those with SRF +/- ORL fluid, we could not confirm this finding.⁹ Likewise, we found no other associations between age of presentation and features of the disc pit itself.

Baseline visual acuity was not predictive of anatomic or visual success but post-operative visual acuity was closely related to the pre-operative vision i.e. the better the baseline vision the better the final vision. A period of observation was carried out in 75% of the eyes but only resulted in any visual or anatomical improvement in 2. This was the case for all fluid distribution types including those without any SRF. This may be partly due to a case ascertainment bias towards those undergoing surgery but suggests that observation rarely results in visual improvement as outlined by other authors^{38, 39}. Importantly observation resulted in reduced vision in 6 patients with a possible effect on final visual outcome. It is also important to note that prior to surgery, laser alone was attempted in 5 patients with no improvement in anatomy or vision.

Previous papers have suggested that the presence of an outer retinal defect at the fovea is associated with a poor visual outcome but we did not confirm this, and also symptom duration was unrelated to the presence of an outer retinal defect.⁸

We did not find any clear benefit of one surgical technique over another, which is also true of the literature to date. The commonest technique was vitrectomy and gas with laser around the temporal peri-papillary border, recently proposed as the logical treatment choice by Jain and Johnson.² Short and long acting gases were used in approximately equal number of cases and laser carried out in 70% of the patients. It is interesting that there was no significant effect on outcome in the cases where laser was not carried out. There was no significant difference in either fluid extent or OCT fluid distribution between the with and without laser group but it is possible that other factors influenced the treatment choice which could have affected outcome. It is noteworthy that laser and intravitreal gas injection alone, without vitrectomy was carried out successfully in two patients with SRF and OLF.

Visual success was achieved in 64% of our cases, with a mean visual gain of almost 3 lines, but complete anatomic success was only achieved in 36% of the cases, lower than our synthesis of the literature. We had a higher proportion of cases with MLF which may partly explain this. We were unable to ascertain the extent of fluid in the published cases and that may have also influenced the comparison. Certainly, any future comparison of surgical approaches to ODPM should match cases for the extent and type of fluid. Furthermore, other authors have noted that fluid resolution after surgery can be very protracted and although the mean follow up in this series was 26 months, the minimum was 6 months,

meaning that some of the cases with short follow up may yet have anatomic success. The follow up duration in the current series was not however statistically different to the literature collected series.

This study has several weaknesses relating to its retrospective design, including a risk of selection bias. Some details of potential interest such as the presence of a posterior vitreous detachment, or glial tissue at the vitreous entrance to the pit, were not consistently recorded so could not be analysed.^{40,41} Although this study is small, ODPM is a rare condition and this is one of the largest series published to date. Both of the significant prognostic factors that we found were corroborated by our synthesis of the literature.

In conclusion we found that in patients with ODPM, the presence of SRF + multilayer intra-retinal fluid as well as the presence of macular fluid extending up to and beyond the macular arcade vessels were negative prognostic factors for visual and anatomical success. Knowledge of prognostic factors may refine the management of ODPM, including selection of the optimum treatment choice. There is clear need for prospective studies on this rare condition, investigating further prognostic factors and the response to differing treatment modalities.

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Figure Legend

Figure 1

Fundal photographs and spectral domain OCT images of four representative cases

A Subretinal fluid and outer retinal layer fluid

B Subretinal fluid only

C Intra-retinal fluid only

D Multi-layered intra-retinal fluid and subretinal fluid

